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MEMORANDUM

SUBJECT: Review of the Office of Pesticide Programs (OPP) draft glyphosate risk assessment and the Cancer Assessment Review Committee (CARC) final report on the carcinogenic potential of glyphosate

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Thank you for the opportunity to review the Office of Pesticide Programs (OPP) draft glyphosate risk assessment and the Cancer Assessment Review Committee (CARC) final report on the carcinogenic potential of glyphosate. The goal of the review is to provide input for a discussion of its cancer classification, with emphasis on the underlying rationale explaining the differences between CARC classification and that of the International Agency for Research on Cancer (IARC). While I was a contributor to the writing of the recent IARC Monograph on glyphosate, I was not able to attend the meeting in Lyon and did not take part of the discussions and deliberations on the appropriate classification. The information in this memorandum is based on my comparison of the three documents: IARC Monograph, Report of the Cancer Assessment Review Committee ("CARC Final Report"), and Draft Human Health Risk Assessment in Support of Registration Review ("Draft Risk Assessment").

A comprehensive comparison the IARC evaluation and the CARC evaluation in the form of a PowerPoint document has been developed by OCSPP and distributed. That document summarizes the data evaluated by both groups (i.e., specific epidemiology, experimental animal, and mutagenicity studies), the interpretation of the results of those studies by the two groups, and the approach (i.e., "weight of evidence" vs "IARC preamble") used for assigning categories. The information presented in that document is comprehensive and this review is intended to supplement rather than reiterate that information. In addition, evaluations in the Draft Human Health Risk Assessment in Support of Registration Review will also be discussed, where appropriate.

Epidemiology: IARC concluded that there was *limited evidence* in humans for the carcinogenicity of glyphosate, which seems to aptly describe the findings across the body of literature: positive association

found in only a small fraction of available studies, and low odds ratios (often with large confidence intervals) when associations were found. CARC argued that those particular limitations together with limitations inherent to virtually all epidemiological studies of agricultural workers (e.g., poor exposure assessment, exposure to multiple toxic agents, lack of a specific *a priori* hypothesis) render the positive results non-informative. The authors of the CARC report reasonably point out that the simultaneous investigation of several different pesticides and several different outcomes without an adjustment for multiple comparisons may increase the chances of observing a spurious significant result. Where they seem to be reaching, in my opinion, is their assertion that recall bias is likely to result in differential misclassification and spurious positive associations. It may be more reasonable to expect non-differential exposure misclassification due to the poor exposure assessment, which would lead to attenuation (or downward bias) of any existing correlation between exposure and effect. The CARC report seems to suggest (on page 38) that any epidemiological evidence short of that which definitively proves "causation" is of little worth. Critics may point out that it is this same logic regarding scientific uncertainty that allowed lead paint to be marketed in the U.S. until 1978 whereas it was restricted in some other industrialized countries as early as the 1920s. The Draft Risk Assessment likewise discounts all epidemiology studies as being insufficiently rigorous to be considered, based largely on the arguments presented in the CARC report.

Animal carcinogenicity tests: IARC reported that glyphosate induced: (1) a positive trend in the incidence of a rare renal tubule carcinoma tumor in male CD-1 mice; (2) a positive trend for hemangiosarcoma also in male CD-1 mice; (3) increased pancreatic islet-cell adenoma in male Sprague-Dawley rats in two studies; and (4) the promotion of skin tumors in an initiation-promotion study in mice when administered as a formulation. [Contradictorily, the monograph states (on page 34) that the fourth study was inadequate for evaluation.] IARC also reported on a number of other studies that found no significant increase in tumor incidence at any site. In contrast, CARC concluded that there was no evidence of any treatment-related increases in the occurrence of any tumor type in either sex of Sprague Dawley or Wistar rats or CD-1 mice in any of the eleven carcinogenicity studies it evaluated. Whereas IARC found a significant increase with a dose-related trend in the renal tube carcinoma (a type of tumor reported in only 0.14% of CD-1 male mice in a historical database), CARC questioned the biological significance based on several factors including the very small number of tumors (not enough to be significantly different than the zero observed in controls), lack of a concurrent increase in non-neoplastic lesions, and a lack of reproducibility in other studies with the same strain of mice. Very similar reasons were cited by CARC for determining the significant trend in hemangiosarcoma to be unrelated to treatment. Regarding the increase in pancreatic islet-cell adenoma, CARC pointed out that there was no dose-related trend, that the incidence was within historical frequencies, and that a number of other factors cast doubt on the study results.

Importantly, there is a set of data that was considered by CARC and acknowledged, but not considered, by IARC. The set consists of five long-term bioassays conducted by registrants and reported in a review by Greim et al. (2015). IARC claimed that it was unable to evaluate the studies due to the limited experimental data provided in the article and supplemental materials. The Greim et al. review may be considered controversial because of its authorship, which includes two members of the Glyphosate Task Force (a consortium of European agrichemical companies whose function is to defend and promote glyphosate), one of whom is an employee of Monsanto (the manufacturer of Roundup-brand glyphosate formulations and Roundup-ready glyphosate-tolerant crop seeds). The extent to which the Greim et al. studies factored into the CARC weight-of-evidence evaluation is unclear as several parts of the CARC report mention that those studies were evaluated [including a statement on page 12 that "This assessment by the CARC includes… a subset of animal studies reported in a review article by Greim et al.

(2015) but not reviewed by IARC"] but a statement on page 39 seems to state the four of the five studies were not included in the weight of evidence assessment. It seems that being clear upfront about not including four of the five Greim et al. studies (if that is indeed the case) might save the CARC report authors from unnecessary criticism.

Mutagenicity/genotoxicity: IARC characterizes the evidence for genotoxicity caused by glyphosate-based formulations as strong based on chromosomal damage in humans observed after aerial spraying and supported by largely positive results in human cells *in vitro* and in mammalian models. CARC found that the vast majority of genotoxicity tests were negative and concluded that there is no convincing evidence of direct DNA damage from glyphosate exposure. A key difference between the two groups is that IARC included tests/observations with glyphosate-based formulations (which also include surfactants) and CARC restricted itself to tests using only the active ingredient. While restricting to only the active ingredient is a reasonable way to ensure that the chemical of interest is causing (or not causing) specific effects, from a human health perspective it is difficult to ignore that individuals are exposed to the formulations and not merely to the active ingredient.

FQPA Safety Factor: While not relevant to either the IARC monograph or CARC report, the Draft Risk Assessment recommends that the FQPA Safety Factor for infants and children be reduced to 1x (effectively eliminated). The recommendation is based on the results of various bioassays (including the neurotoxicity battery, pre-natal developmental toxicity studies, and two-generation reproduction toxicity studies). The FQPA statute authorizes EPA to replace the default tenfold "FQPA safety factor" with a different factor only if reliable data demonstrate that the resulting level of exposure would be safe for infants and children. Since the purpose of the safety factor is to account for toxicological data deficiencies, eliminating the safety factor suggests that the existing data are complete enough to unequivocally demonstrate that infants and children are no more vulnerable than adults. As the conflicting interpretations of carcinogenicity data by IARC and CARC (as described above) show, it may be reasonable for other evaluators to interpret the existing neurodevelopmental data such that the data call for a safety factor for infants and children above 1x. Given the controversy surrounding glyphosate and its use with genetically modified herbicide-resistant crops and the fact that it is *always* used in combination with surfactants (often with unknown toxicity), the precedent for assigning a 1x safety factor should be explicitly stated and the similarities of the data detailed.